

REMARKS

Claims 1-23 were pending. Claims 9-13 and 18-23 were withdrawn from consideration as directed to non-elected inventions. Claims 1-8 and 14-17 were rejected. New claim 24 was added. Claim 3 was amended. Upon entry of this amendment, claims 1-8, 14-17, and 24 will be pending.

Claim 3 was amended to correct its dependency.

New claim 24 was added. Support for claim 24 can be found throughout the specification including, *inter alia*, on page 7, lines 1-26.

No new matter has been added.

Summary of Invention

The present application provides modified TNF comprising TNF covalently bound to between about five and twelve PEG molecules, each PEG molecule having an approximate weight average molecular weight in the range of about 10,000 to about 40,000.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-8 and 14-17 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the recitation of "molecular weight in the range of about ..." because there are no units associated with the molecular weight range. Because one of skill in the art would readily understand the instant usage of the term in the claims, Applicants respectfully disagree.

The proper inquiry, when determining whether a claim satisfies the requirements of 35 U.S.C. § 112, second paragraph, is a determination "whether those skilled in the art would understand what is claimed when the claim is reading light of the specification." *Orthokinetics Inc. v. Safety Travel Charis, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

Those of ordinary skill in the art would readily understand the meaning and usage of the phrase PEG molecules "having an average weight of about 10,000 to 40,000." PEG, commercially available from many chemical companies, is listed in catalogues

without the use of molecular weight units. For example, the 1999/2000 Fluka catalog lists the compound "Polyethylene glycol standard 20,000" (product number 81928) with no units associated with the molecular weight in the product description and refers to PEG molecules with an average molecular weight of 20,000. (A copy of the Fluka catalog listing is attached hereto).

Applicants further note that on page 3 of the specification, Applicants refer to the Tsutsumi *et al.* (JPN J. Cancer Res., **85**, pp.9-12, 1994, hereinafter "Tsutsumi"). and discuss the use therein of PEG 5000. This discussion also does not associate a molecular weight unit with the specific PEG but would be understood by the art-skilled. Tsutsumi also fails to associate a molecular weight unit with a specific PEG; for example, describing the identity and source of the PEG used as "PEG (Mw 5,000; Aldrich Chemical Co., Wisconsin, USA)." (see Tsutsumi *et al.* page 9, right column).

Therefore, the claims do particularly point out and distinctly claim the subject matter that is put forth in claims 1-8 and claims 14-17. In view of the foregoing, Applicants respectfully request that the rejection of claims 1-8 and 14-17 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Claim 3 was rejected under 35 U.S.C. § 112, second paragraph, because it recites the term "said linker" without proper antecedent basis. Applicants have added claim 24 to provide antecedent basis for claim 3 and have amended claim 3 to depend from claim 24, rendering the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection of claim 3 under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 102(b)

Claims 1-7 and 14-17 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Tsutsumi (JPN J. Cancer Res., **85**, pp.9-12, 1994). The Office Action alleges that Tsutsumi discusses the pegylation of natural human TNF- α with N-succinimidyl succinate PEG. Although Tsutsumi discusses the use of PEG in the conjugate with a molecular weight of only about 5,000, nonetheless, the Office Action alleges that a molecular weight of about 5000 is "an approximate weight average

molecular weight in the range of about 10,000 to about 40,000," as recited in claim 1; "an approximate weight average molecular weight in the range of about 20,000 to about 30,000," as recited in claims 2, 15, and 17; and "an approximate molecular weight in the range of about 20,000 to about 30,000," as recited in claim 16. Applicants respectfully disagree and request that this rejection be withdrawn.

An anticipation rejection requires a showing that each limitation of a claim be found in a single reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). As Tsutsumi fails to teach each limitation of claims 1-7 and 14-17, Tsutsumi fails to anticipate.

Tsutsumi fails to teach a TNF-PEG conjugate wherein the bound PEG has a molecular weight in the range of about **10,000** to about **40,000**, as recited in claim 1. The molecular weights of the bound PEG recited in claims 1, 2, 15, 16, and 17 are on the order of about 2-fold to about 8-fold larger than the PEG is recited in Tsutsumi, PEG-5000. One of ordinary skill in the art would **not** agree that a PEG molecule with a molecular weight of about 5,000 is within the range of about 10,000 to about 40,000, nor is it in the range of about 20,000 to about 30,000. Such an assertion is analogous to the suggestion that an individual weighing 100 pounds falls in the weight range of about 200 to about 800 pounds, a suggestion bordering on the ridiculous. The Merriam-Webster dictionary defines "about" to mean, "reasonably close to." One of ordinary skill in the art **would not** consider 5,000 to be "reasonably close to" 10,000, less still to 20,000, and even less to 30,000.

Tsutsumi also fails to teach that the TNF is covalently bound to between about five and twelve molecules. Applicants were unable to locate any disclosure in Tsutsumi regarding the number of PEG molecules covalently attached to the TNF.

Applicants further point out that the present application discusses the Tsutsumi reference and distinguishes in the "Background of the Invention" the use of PEG with a molecular weight of 5000 from the present invention. For example, page 3, lines 21-24 of the specification sets forth that "these investigators [Tsutsumi *et al.*] used only PEG with a molecular weight of 5000 (PEG5000) attached to the primary amines on TNF with a succinimidyl succinate linker and failed to determine not only the optimal method of attaching PEG to TNF but also the optimal attachment sites on the molecule." Clearly

Applicants did not consider PEG with a molecular weight of 5,000 to fall within the range of about 10,000 to about 20,000.

If the assertion that a PEG with a molecular weight of 5,000 falls into the range of from about 10,000 to 20,000 is based on the Examiner's personal knowledge, Applicants respectfully request that the Examiner provide an affidavit setting forth the basis of the allegation as required by 37 CFR §1.104(d)(2).

Thus, Tsutsumi fails to teach each and every limitation of claims 1-7 and 14-17. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1 and 8 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Tsutsumi and Nakamura *et al.* (Int. J. Cancer, 48, pp. 744-48, 1991, hereinafter, "Nakamura"). Applicants respectfully disagree.

As is clear from MPEP §2143, in order to provide a *prima facie* case of obviousness, the Examiner must satisfy three criteria.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP §2143. To establish a *prima facie* case of obviousness, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). "In other words, the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998).

Tsutsumi and Nakamura fail to teach the limitations of claims 1 and 8 individually or in combination and, therefore, do not render Applicants' invention *prima facie* obvious. As set forth above, Tsutsumi discusses a pegylated TNF molecule wherein the bound PEG molecule has an average molecular weight of 5,000, which falls outside the molecular weight range of PEG taught by the present invention. The Office Action has failed to provide any motivation for the art-skilled to use PEG molecules having a higher average molecular weight than that discussed in Tsutsumi (e.g. motivation to use PEG 10,000 instead of PEG 5,000).

The Nakamura reference further fails to suggest the TNF recited in claim 8. Nakamura discusses a TNF mutant molecule that has residues 1 to 7 deleted and residues 8, 9, and 10 mutated. The TNF recited in claim 8 is mutated by deleting amino acid residues 1 to 9. The Examiner has failed to provide any motivation to modify the TNF discussed in Nakamura in such a way so as to arrive at the TNF recited in the claim 8.

Furthermore, the Office has failed to provide motivation to those of skill in the art would combine Tsutsumi with Nakamura. However, even if the Office did supply motivation, which it did not, one of ordinary skill would not be in possession of Applicants' invention because either alone or in combination, Tsutsumi and Nakamura fail to teach what the claimed invention. The combination of Tsutsumi and Nakamura fails to provide a TNF conjugated to PEG with a molecular weight of about 10,000 to about 20,000, less still a TNF modified as described in claim 8 conjugated to PEG with a molecular weight of about 10,000 to about 20,000. It appears that the Office has impermissibly used hindsight to combine the two references. Applicants respectfully remind the Examiner that the Office is prohibited from basing an obviousness rejection on hindsight reconstruction by including knowledge "gleaned only from applicants disclosure . . ." *In re McLaughlin*, 170 USPQ 209, 212 (CCPA 1971).

In view of the foregoing, the Applicants' respectfully request that the rejection under 35 U.S.C § 103(a) be reconsidered and withdrawn.

The foregoing represents a *bona fide* attempt to advance the present application to allowance. Applicants respectfully invite the Examiner to contact the undersigned at

(215) 564-8338 to discuss any issues unresolved by this response. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



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Date: August 8, 2002
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Attachments:

Fluka catalog listing
"Version with markings to show changes made"

VERSION WITH MARKINGS TO SHOW CHANGES MADE**In the Claims**

Please add new claim 24 as follows:

24. **(New)** The modified TNF of claim 1 wherein said PEG is covalently bound to primary amine groups on said TNF through a biocompatible linker.

Please amend claim 3 as follows:

3. **(Amended)** The modified TNF of claim [1] 24 wherein said linker is selected from the group consisting of succinimidyl succinate, succinimidyl propionate, and N-hydroxy succinimidyl.

Laboratory Chemicals
and Analytical Reagents

1999/2000



Fluka

Riedel-deHaën

US \$

155

Polyethylene glycol 100'000M_n - 100000 [25322-68-3] EC No 2034733

pract.

Viscosity (5% in H₂O, 20°C) 30-50 mPa.s

CH-Giftkl. free WGK 1

250 g 66.60

Polyethylene glycol Standard 200

[25322-68-3] EC No 2034733

for GPC

M_n - 194, M_w - 194, M_w/M_n - 1.00; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

Rpt. 171°C CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 300

[25322-68-3] EC No 2034733

for GPC

M_n - 330, M_w - 306, M_w/M_n - 1.08; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 400

[25322-68-3] EC No 2034733

for GPC

M_n - 420, M_w - 375, M_w/M_n - 1.06; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 600

[25322-68-3] EC No 2034733

for GPC

M_n - 600, M_w - 550, M_w/M_n - 1.06; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 1'000

[25322-68-3] EC No 2034733

for GPC

M_n - 970, M_w - 900, M_w/M_n - 1.05; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 1'500

[25322-68-3] EC No 2034733

for GPC

M_n - 1500, M_w - 1430, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 2'000

[25322-68-3] EC No 2034733

for GPC

M_n - 2010, M_w - 1900, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 3'000

[25322-68-3] EC No 2034733

for GPC

M_n - 3120, M_w - 2980, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 4'000

[25322-68-3] EC No 2034733

for GPC

M_n - 4450, M_w - 4120, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 6'000

[25322-68-3] EC No 2034733

for GPC

M_n - 6240, M_w - 5850, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 8'000

[25322-68-3] EC No 2034733

for GPC

M_n - 8600, M_w - 8100, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Fluka

Riedel-de Haen

Polyethylene glycol Standard 12'000

[25322-68-3] EC No 2034733

81296 for GPC

Fluka

M_n - 12000, M_w - 10800, M_w/M_n - 1.1600, M_w/M_n - 1.04; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 17'500

[25322-68-3] EC No 2034733

81297 for GPC

Fluka

M_n - 16000, M_w - 12800, M_w/M_n - 1.4100, M_w/M_n - 1.10; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 20'000

[25322-68-3] EC No 2034733

81298 for GPC

Fluka

M_n - 23000, M_w - 21200, M_w/M_n - 2.2500, M_w/M_n - 1.06; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 99.10

Polyethylene glycol Standard 35'000

[25322-68-3] EC No 2034733

81299 for GPC

Fluka

M_n - 40000, M_w - 36500, M_w/M_n - 4.1500, M_w/M_n - 1.14; The exact values can be taken from the accompanying Certificate of Analysis

Merck: 12, 7729

CH-Giftkl. free WGK 1

1 g 92.60

Polyethylene glycol Standard 330 certified according to DIN

[25322-68-3] EC No 2034733

03461 for GPC

Fluka

M_n - 330, M_w - 306, M_w/M_n - 1.08; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 420 certified according to DIN

[25322-68-3] EC No 2034733

03462 for GPC

Fluka

M_n - 420, M_w - 375, M_w/M_n - 1.06; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 600 certified according to DIN

[25322-68-3] EC No 2034733

03463 for GPC

Fluka

M_n - 600, M_w - 550, M_w/M_n - 1.06; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 1'000 certified according to DIN

[25322-68-3] EC No 2034733

03464 for GPC

Fluka

M_n - 970, M_w - 900, M_w/M_n - 1.05; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 2'000 certified according to DIN

[25322-68-3] EC No 2034733

03465 for GPC

Fluka

M_n - 2010, M_w - 1900, M_w/M_n - 1.9600, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 3'100 certified according to DIN

[25322-68-3] EC No 2034733

03466 for GPC

Fluka

M_n - 3120, M_w - 2980, M_w/M_n - 3.0600, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 4'400 certified according to DIN

[25322-68-3] EC No 2034733

03467 for GPC

Fluka

M_n - 4450, M_w - 4120, M_w/M_n - 4.2400, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70

Polyethylene glycol Standard 6'200 certified according to DIN

[25322-68-3] EC No 2034733

03468 for GPC

Fluka

M_n - 6240, M_w - 5850, M_w/M_n - 6.0000, M_w/M_n - 1.03; The exact values can be taken from the accompanying Certificate of Analysis

RTECS TQ4030000 CH-Giftkl. free WGK 1

1 g 153.70